Remarks

Status

Claims 60-62, 71-75 and 81-96 are presently pending. Applicants have canceled claims 81, 84, 85, 88, 91 and 94-96 without prejudice to the filing of any appropriate continuation applications. Claims 60-62 and 71-75 stand rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. Claims 60-62, 71-75 and 81-96 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Applicants gratefully acknowledge that the drawings filed on 26 April 2000 have been accepted. Applicants also gratefully acknowledge that the objection to the specification has been withdrawn, and that the rejection of claims 60-62, 71-75 and 81-96 under 35 U.S.C. § 112, second paragraph has been withdrawn.

Claims 60, 61, 62, 71 and 82 have been amended to recite a "human" PMS2 mismatch repair protein. Claims 60, 61, 62 and 71 were further amended to recite "wherein the protein comprises the first 133 amino acids of human PMS2." Support for these amendments can be found at least in canceled claim 84. Claims 82, 89 and 92 were amended to correct dependencies.

The amendments presented herein add no new matter and do not raise new issues requiring further search. Applicants respectfully request entry and consideration of the foregoing amendments, which are intended to place this case in condition for allowance, or at least in better condition for appeal. Entry of the amendment under Rule 116 is requested.

The Rejection of the Claims Under 35 U.S.C. § 112, ¶ 1

New matter

Claims 60-62 and 71-75 stand rejected as failing to comply with the written description requirement. The new recitation in claims 60-62 and 71 of "a dominant negative form of a PMS2 mismatch repair protein" is said to be new matter not supported by the specification. The Office Action states that the instant specification does not teach, generically, any dominant negative mutation of PMS2 other than truncation following amino acid 133 of human PMS2 (page 3). The Office Action concludes that, while an understanding of how the disclosed invention operates is not essential, extrapolation of the disclosed species to the claimed breadth of dominant negative PMS2 mismatch repair genes requires a structural/functional correlation that would allow one of skill in the art to envision dominant negative mutations other than a truncation following amino acid 133 of human PMS2. Applicants respectfully traverse this rejection based on the amended claims now presented.

The amended claims are directed in part to a dominant negative form of a ***human*** PMS2 mismatch repair protein, wherein the protein comprises ***the first 133 amino acids of human PMS2***. The specification, coupled with what was known in the art at the time of filing regarding human PMS2-134 provides sufficient structure and function to demonstrate to those of skill in the art that the inventors had possession of the full scope of the currently amended claims.

The instant specification more than adequately describes the claimed invention. Applicants teach the cDNA and protein sequences of human PMS2 (SEQ ID NO:s 1 and 2, respectively). Applicants' specification teaches that a germ-line truncating mutation of the *hPMS2* gene at codon 134 was identified in a patient having Hereditary Nonpolyposis Colorectal Cancer Syndrome, a disease that is known to involve genetic instability due to defective

mismatch repair (page 1, lines 12-13; page 11, lines 6-7). Applicants teach that the human form of the truncated protein (PMS2-134), when expressed by a vector in SH cells, caused perturbations in the endogenous mismatch repair machinery that resulted in deletions or insertions that changed the reading frame (specification, page 12, lines 24-27; Figure 2). Further, nuclear extracts from clones expressing PMS2-134 demonstrated defects in 5' repair activity (specification, page 17, lines 15-17; Table 2). Finally, the Office Action admits that the specification teaches a dominant negative mutation of PMS2 that is a truncation following amino acid 133 of human PMS2 (page 3, first full paragraph; page 4, first partial paragraph).

When read as a whole, taking into account the knowledge of persons skilled in the art at the filing date of the instant application, this specification indicates to those skilled in the art that Applicants had possession of the claimed subject matter at the time of filing. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection of claims 60-62 and 71-75 under 35 U.S.C. § 112, first paragraph.

Enablement

Claims 60-62, 71-75, and 81-96 stand rejected as not supported by an enabling disclosure for their full scope. The Office Action asserts that there is no guidance in the specification as originally filed as to how to mutate any other PMS2 gene other than the human PMS2 gene described in the specification or how to mutate human PMS2 in any way other than truncation of human PMS2 at amino acid 134 since the structural and functional correlation is not understood or taught by the specification (page 6). Enablement is said to be limited to a transgenic mouse whose germ and somatic cells all comprise a transgene encoding a dominant negative human PMS2-134 gene product wherein when the transgene is expressed, the cells expressing the

transgene exhibit hypermutability (page 4). Without acquiescing to the rejection, the pending claims were amended to conform to the scope that the Examiner acknowledges is enabled.

Because the dominant negative effect of human PMS2-134 is well characterized, Applicants respectfully submit that one of ordinary skill in the art could easily use the claimed human PMS2 mismatch repair protein comprising the first 133 amino acids of hPMS2 to make transgenic mice without undue experimentation using routine techniques. As discussed above, Applicants teach the cDNA sequence encoding the human PMS2 protein, as well as the amino acid sequence of the PMS2 protein. Applicants teach how to make hypermutable, transgenic mice expressing a dominant negative form of the human PMS2 mismatch repair protein comprising the first 133 amino acids of hPMS2 (page 9, line 21 to page 10, line 6). Determining whether a mouse or a fertilized mouse egg expresses the claimed human PMS2 protein comprising the first 133 amino acids of hPMS2 and determining whether it exerts a dominant negative effect would involve only routine screening.

For at least these reasons, Applicants' specification, coupled with the level of skill in the art, enables a person of skill in the art to make and/or use the claimed invention across its full scope. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 60-62, 71-75, and 81-96 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

All issues, objections, and rejections of the office action have been addressed. It is respectfully urged that the claims are now in condition for allowance. Should there be any remaining issues, the examiner is invited to contact the undersigned directly.

Respectfully submitted,

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